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Detouring adrenergic stimulation to induce adipose thermogenesis

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Abstract

Harnessing the thermogenic, energy-expending capacity of adipocytes has the potential to combat metabolic disorders. Although β_3 -adrenergic receptor agonists are the best-known activators of thermogenesis, they carry considerable cardiovascular risks. A new study demonstrates the ability of G protein-coupled receptor 3 to intrinsically drive adipose thermogenesis independent of β_3 -adrenergic receptor signalling.

Canonical means of triggering thermogenic programming in adipocytes via G protein-coupled receptors (GPCRs) involve the β -adrenergic receptors (ADRB1, ADRB2 and ADRB3). Upon ligand binding (for example, noradrenaline), β -adrenergic receptors mediate Gs-coupled production of cAMP using adenylyl cyclase¹ (Fig. 1a). This increase in levels of cAMP subsequently activates pathways involved in glucose uptake, β -oxidation, lipid mobilization and uncoupling of the electron transport chain to ultimately convert chemical energy to heat². In theory, modulating this pathway with β_3 -adrenergic receptor agonists would seem to be a feasible strategy to counteract metabolic disease. As *Adrb3* is predominantly expressed in adipocytes, it has long been thought that its stimulation would decrease adipose tissue mass with limited off-target effects¹. Unfortunately, pharmacological activators of β_3 -adrenergic receptors, such as mirabegron, increase blood pressure and are associated with cardiovascular risks at a clinically effective dose, thus precluding their use². This probability of cardiovascular risk is amplified in metabolic disorders³. To that end, a 2020 study in humans indicates the role of alternative mechanisms, such as β_2 -adrenergic stimulation, for adipose thermogenesis and lipolysis⁴. However, these studies are in their infancy compared to what is known on β_3 -adrenergic agonists, and it remains to be seen whether they can be translated to improved clinical outcomes.

Previous work has focused on the discovery of non-canonical pathways to activate thermogenic adipocytes³; however, Sveidahl Johansen et al. postulate that factors impacting the transcriptional control of GPCRs themselves should be acknowledged². The intrinsic and ligand-independent roles of GPCRs are often overlooked, as are factors that modulate the expression of these key plasma membrane constituents. GPR3, GPR6 and GPR12 have

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Competing interests

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long been recognized as constitutively active GPCRs that are highly expressed in the central nervous system⁵. GPR3, in particular, is important for neurological processes, such as neurite outgrowth and the production of amyloid- β ⁵. However, we are only scratching the surface in our understanding of factors that affect the transcriptional control of these constitutively active GPCRs⁶.

In their excellent study, Sveidahl Johansen and colleagues demonstrate that *Gpr3* expression is cold-induced by way of a non-canonical lipolytic signal that is sufficient to promote the thermogenic programme in both brown and beige adipocytes from mouse models of metabolic disease and in humans². Using a targeted qPCR array, they examined 44 Gs-coupled receptors in mice at thermo-neutrality (29°C) and following cold exposure (4°C) and found that GPR3 was the most profoundly cold-induced receptor in subcutaneous white adipose tissue and brown adipose tissue (BAT)². Indeed, both the gene and the protein were upregulated in these thermogenic adipose depots. To confirm that GPR3 signalling was independent of β -adrenergic agonism, they blunted this signalling pathway using β -less mice where *Adrb1*, *Adrb2* and *Adrb3* were genetically ablated. The researchers noted an additional increase in the expression of GPR3 at both room temperature and in the cold, further affirming the importance of this GPCR in mouse adipose tissue².

To illustrate the role of GPR3 in vivo, the authors created a model in which *Gpr3* is over-expressed in brown and beige adipocytes and found that these mice had statistically significantly lower body and tissue weights than controls². This finding was true not only of the subcutaneous white adipose tissue and BAT but also in the epididymal white adipose tissue, which does not exhibit UCP1-mediated thermogenesis². When fed with a high-fat diet, transgenic mice overexpressing GPR3 in thermogenic adipose depots were protected from developing diet-induced obesity despite similar levels of food intake². Moreover, transitioning to a high-fat diet increased energy expenditure in the transgenic mice and lowered the respiratory exchange ratio, suggesting that dietary lipids are fuelling GPR3-dependent thermogenesis². These animals benefited from increased glucose tolerance and protection against ectopic lipid deposition in the liver versus wild-type controls². Interestingly, their findings build upon the results of a previous report that demonstrated that whole-body *Gpr3*-knockout mice had poor thermogenic gene expression and were prone to age-related obesity⁷. To examine a link with human obesity, Sveidahl Johansen et al. measured GPR3 expression in the supraclavicular BAT of volunteers and noted that higher expression of this receptor is associated with lower BMI in glucose-tolerant individuals compared with samples from individuals with impaired glucose control². This finding was supported by in vitro studies of human brown adipocytes in which knockdown of *GPR3* dramatically reduced UCP1 expression².

Conversely, when the researchers applied CRISPR–Cas9 engineering to drive expression of GPR3 in human subcutaneous white adipocytes, they observed an increase in both fatty acid uptake and mitochondrial leak respiration as well as the induction of thermogenic genes such as *UCP1* and *PRDM16*. Collectively, these results suggest that GPR3 expression can stimulate adipocyte browning in and of itself, an alternate route to the well-known noradrenaline-mediated pathway. Although the GPR3-mediated thermogenic programming outlined in this study is ligand-independent, it does rely on an unidentified lipolytic signal

(Fig. 1b), as a double knockout of adipose triglyceride lipase and hormone-sensitive lipase greatly reduced cold-induced GPR3 expression². This finding is in line with other findings demonstrating that genetic ablation of lipolysis diminishes thermogenic activation^{8,9}. Although this manuscript demonstrated the intrinsic ability of GPR3 to trigger thermogenesis, future studies should seek to elucidate the nature of the lipolytic signal (or signals) affecting its transcriptional control. For example, a 2018 study showed that 130 lipid species were changed in BAT from cold-challenged mice¹⁰. In particular, they found that phosphatidylglycerol and cardiolipin metabolism were activated, suggesting potential candidates for further exploration¹⁰. There is also the question of which mechanistic path is triggered by the lipolytic signal to induce GPR3 expression, as Sveidahl Johansen and colleagues used small interfering RNA-mediated knockdown of PPAR α , PPAR γ and known lipid-activated nuclear receptors in brown adipocytes but did not prevent noradrenaline-induced upregulation of *Gpr3* (reF.²). The exciting answers to these questions might lend further credence to the notion that targeting GPR3 via activators of lipolysis is a feasible strategy for mitigating the impact of metabolic disease.

References

1. Cero Cet al. β 3-Adrenergic receptors regulate human brown/beige adipocyte lipolysis and thermogenesis. *JCI insight*6, 139160 (2021). [PubMed: 34100382]
2. Sveidahl Johansen Oet al. Lipolysis drives expression of the constitutively active receptor GPR3 to induce adipose thermogenesis. *Cell*10.1016/j.cell.2021.04.037 (2021).
3. Chen Yet al. Thermal stress induces glycolytic beige fat formation via a myogenic state. *Nature*565, 180–185 (2019). [PubMed: 30568302]
4. Blondin DPet al. Human brown adipocyte thermogenesis is driven by β 2-AR stimulation. *Cell Metab.* 32, 287–300 (2020). [PubMed: 32755608]
5. Laun AS, Shrader SH, Brown KJ & Song Z-H GPR3, GPR6, and GPR12 as novel molecular targets: their biological functions and interaction with cannabidiol. *Acta Pharmacol. Sin* 40, 300–308 (2019). [PubMed: 29941868]
6. Hauser AS, Attwood MM, Rask-Andersen M, Schiöth HB & Gloriam DE Trends in GPCR drug discovery: new agents, targets and indications. *Nat. Rev. Drug Discov* 16, 829–842 (2017). [PubMed: 29075003]
7. Godlewski Get al. Mice lacking GPR3 receptors display late-onset obese phenotype due to impaired thermogenic function in brown adipose tissue. *Sci. Rep*5, 14953 (2015). [PubMed: 26455425]
8. Kaur Set al. Adipose-specific ATGL ablation reduces burn injury-induced metabolic derangements in mice. *Clin. Transl Med*11, e417 (2021). [PubMed: 34185433]
9. Haemmerle Get al. Defective lipolysis and altered energy metabolism in mice lacking adipose triglyceride lipase. *Science*312, 734–737 (2006). [PubMed: 16675698]
10. Lynes MDet al. Cold-activated lipid dynamics in adipose tissue highlights a role for cardiolipin in thermogenic metabolism. *Cell Rep.* 24, 781–790 (2018). [PubMed: 30021173]

Fig. 1 | An alternative paradigm for the activation of adipose thermogenesis.

A simplified figure depicting the key differences between canonical thermogenesis (part **a**) and G protein coupled receptor 3 (GPR3)-mediated intrinsic thermogenic programming (part **b**). **a** | Cold induces the release of noradrenaline (mediated by the sympathetic nervous system), which binds to β -adrenergic receptors to stimulate cAMP production, leading to upregulation of thermogenic genes via protein kinase A (PKA). **b** | The mechanism discovered by Sveidahl Johansen et al. demonstrates that a GPCR ligand is unnecessary. Rather, a hitherto unidentified lipolytic signal greatly increases the expression of GPR3, which promotes cAMP production via its intrinsic N-terminal activity. ADRB1–3, β -adrenergic receptors; UCP1: uncoupling protein 1.